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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,556	04/14/2005	Octavian Schatz	BOH6278P0150US	2322

32116 7590 04/16/2008

WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
500 W. MADISON STREET
SUITE 3800
CHICAGO, IL 60661

EXAMINER
THOMAS, DAVID C

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
04/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,556	SCHATZ ET AL.	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03 January 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of the enzyme Eco31I with traverse, in the reply filed on July 21, 2007 is acknowledged. Claims 23-36 and 38-44 (previously presented) and claim 37 (currently amended) will be examined on the merits. Claims 39-44 were previously canceled. The traversal is on the grounds that claim 37 does not lack unity, but in fact the two restriction enzymes, Eco31I and Esp3I have a common property or activity and belong to the same recognized class of chemical compounds. Furthermore, Applicant argues that the two enzymes, though not having identical structures, do have common activities and act on very similar recognition sites. The Examiner agrees with this argument and therefore the species restriction is withdrawn.

Specification

2. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

3. The abstract of the disclosure is objected to because it is not in the form of a single paragraph and exceeds both 150 words and a single page. Correction is required. See MPEP § 608.01(b).

Claim Interpretation

4. Prior to examination of the claims, the claims must first be construed. In several of the claims, a multi-step method for the manufacture of a nucleic acid is cited. However, there is no strict requirement in the claims for a particular order of the steps of the invention, and thus any teaching in the specification may not be read into a claim when the claim language is broader than the embodiment.

Applicants are directed to MPEP Section 2111.01, part II:

>II. IT IS IMPROPER TO IMPORT CLAIM LIMITATIONS FROM THE SPECIFICATION

"Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment." Superguide Corp. v. DirecTV Enterprises, Inc., 358 F.3d 870, 875, 69 USPQ2d 1865, 1868 (Fed. Cir. 2004). See also Liebel-Flarsheim Co. v. Medrad Inc., 358 F.3d 898, 906, 69 USPQ2d 1801, 1807 (Fed. Cir. 2004)(discussing recent cases wherein the court expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment);< E-Pass Techs., Inc. v. 3Com Corp., 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) ("Interpretation of descriptive statements in a patent's written description is a difficult task, as an inherent tension exists as to whether a statement is a clear lexicographic definition or a description of a preferred embodiment. The problem is to interpret claims in view of the specification' without unnecessarily importing limitations from the specification into the claims."); Altiris Inc. v. Symantec Corp., 318 F.3d 1363, 1371, 65 USPQ2d 1865, 1869-70 (Fed. Cir. 2003) (Although the specification discussed only a single embodiment, the court held that it was improper to read a specific order of steps into method claims where, as a matter of logic or grammar, the language of the method claims did not impose a specific order on the performance of the method steps, and the specification did not directly or implicitly require a particular order).

Thus, references that teach all the steps of claims, even if in a different order, will be considered to anticipate the claims.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 23-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Schatz (WO 00/75368).

With regard to claims 23-25, 30 and 31, Schatz teaches a method for the manufacture of a nucleic acid molecule (for summary, see p. 3, line 30 to p. 4, line 8) comprising the steps of;

a) providing a first at least partially double-stranded oligonucleotide which has a modification allowing the oligonucleotide to be coupled to a surface, whereby the oligonucleotide comprises a recognition site for a first type IIS restriction enzyme which cuts outside its recognition site, and which oligonucleotide comprises a single-stranded overhang (a hairpin oligonucleotide, anchor oligo, is provided with a single-stranded overhang, a modification such as biotin for coupling to a surface and restriction site for a type IIS restriction endonuclease, p. 4, lines 12-16, p. 8, lines 6-12, Figure 1, top and Figures 9 and 10);

b) providing a second at least partially double-stranded oligonucleotide whereby the oligonucleotide comprises a recognition site or a part thereof or a sequence which is complementary thereto, for a second type IIS restriction enzyme which cuts outside its recognition site, and which second oligonucleotide comprises a single-stranded

overhang (a second hairpin oligonucleotide, splinker oligo, is provided with a single-stranded overhang, and a restriction site for a type IIS restriction endonuclease, p. 4, lines 12-16, p. 8, lines 17-22, Figure 1, top and Figure 12);

c) ligating the first and the second oligonucleotide via their overhangs generating a first ligation product (hairpin oligonucleotides are ligated after hybridization of their overhangs, p. 4, lines 23-25 and Figure 1, second panel);

d) immobilising the first ligation product to the surface via the modification (the anchor oligo binds to a solid surface through the biotin moiety, (the ligation product can bind via the anchor oligo though a biotin moiety to solid matrix such as a bead containing streptavidin, p. 13, lines 13-19 and 24-29);

e) cutting the immobilised ligation product with the first type IIS restriction enzyme thus releasing an elongated oligonucleotide having an overhang (the ligation product is cleaved by treatment with a type II restriction enzyme such as Eco31I which cleaves outside the recognition sequence to release an elongated product containing an overhang, with part of the anchor sequence remaining with the splinker sequence, p. 4, lines 28-31, p. 15, line 28 to p. 16, line 8, , p. 17, lines 22-25, Figure 1, third panel and Figure 12);

f) combining the elongated oligonucleotide with a further at least partially double-stranded oligonucleotide which has a modification allowing the oligonucleotide to be coupled, to a surface, whereby the further oligonucleotide comprises a recognition site for a further type IIS restriction enzyme which cuts outside its recognition site and which oligonucleotide comprises a single-stranded overhang, and ligating the elongated

second oligonucleotide and the further at least partially double-stranded oligonucleotide via their overhangs forming a further ligation product (the lengthened splinker oligo is transferred to a new reaction container and bound to a new anchor oligo via the overlapping regions for further ligation, p. 16, lines 8-10, p. 17, lines 25-29 and Figure 1, fourth panel);

g) immobilising the further ligation product to a surface via the modification (the ligation product can bind via the anchor oligo through a biotin moiety to a solid matrix such as a bead containing streptavidin, p. 13, lines 13-19 and 24-29);

h) cutting the further ligation product with the further type IIS restriction enzyme releasing an elongated oligonucleotide having an overhang (the ligation product can then be cleaved with a restriction endonuclease specific to the anchor oligo to yield a lengthened splinker product, p. 18, lines 1-3); and

i) optionally, repeating steps f) to h) (cycle of ligation, cleaving, and washing allows another cycle to start and produce increasingly longer products, p. 16, lines 14-17 and Figure 1, bottom panel).

With regard to claims 26 and 27, Schatz teaches a method wherein the overhang is a 5'-overhang or a 3'-overhang of 1-7 nucleotides (5'-overhangs of four nucleotides are produced with restriction enzymes Esp3I, Bpi I or BsaI, p. 15, line 28 to p. 16, line 10 and Figures 9, 10 and 12).

With regard to claim 28, Schatz teaches a method wherein the elongated oligonucleotide is transferred to a new reaction vessel where it is combined with the further oligonucleotide (the lengthened splinker oligo is transferred to a new reaction

container and bound to a new anchor oligo via the overlapping regions for further ligation, p. 16, lines 8-10, p. 17, lines 25-29 and Figure 1, fourth panel).

With regard to claim 29, Schatz teaches a method wherein the at least partially double-stranded oligonucleotide comprises a constant region and a variable region whereby the constant region contains a recognition site for a type IIS restriction enzyme, and the variable region contains a nucleic acid sequence which corresponds to a part of the nucleic acid sequence of the nucleic acid molecule to be manufactured (the first and second partially double-stranded oligonucleotides comprise a constant region of a recognition site for a second type IIS restriction enzyme, and which second oligonucleotide comprises a single-stranded overhang (a second hairpin oligonucleotide, splinker oligo, is provided with a single-stranded overhang, and a restriction site for a type IIS restriction endonuclease, p. 4, lines 12-16, p. 8, lines 17-22, Figure 1, top and Figure 12).

With regard to claim 32, Schatz teaches a method wherein the overhang generated upon cutting the first oligonucleotide with the first type IIS restriction enzyme is essentially complementary to the overhang of the second at least partially double stranded oligonucleotide (hairpin oligonucletotides are ligated after hybridization of their complementary overhangs, p. 4, lines 23-25, p. 16, lines 8-10 and Figure 1, second panel).

With regard to claims 33 and 41, Schatz teaches a method for the manufacture of a nucleic acid molecule comprising the following steps:

a) providing a first ligation product, whereby the first ligation product consists of a first oligonucleotide moiety comprising a recognition site for a first type IIS restriction enzyme, a second oligonucleotide moiety comprising a recognition site for a second type IIS restriction enzyme and a third oligonucleotide moiety, whereby the third oligonucleotide moiety is a part of the nucleic acid molecule to be manufactured, and whereby the first and the second type IIS restriction enzymes each generate an overhang (hairpin oligonucleotides, anchor and splinker oligos, are provided, each with a single-stranded overhang and a restriction site for a type IIS restriction endonuclease that generates an overhang, p. 4, lines 12-16, Figure 1, top and Figures 9 and 10; oligonucleotides are ligated to form a ligation product, p. 4, lines 23-25 and Figure 1, second panel; after cleavage, another hairpin oligonucleotide is combined with the cleavage product to form a longer new product, p. 16, lines 8-10, p. 17, lines 25-29 and Figure 1, fourth panel), whereby the overhang generated by the first type IIS restriction enzyme has a length which is different from the length of the overhang generated by the second type IIS restriction enzyme (sets of anchor and splinker oligonucleotides can contain combinations of different restriction enzyme recognition sequences, including those with one-, two- or four-base overhangs, p. 21, line 28 to p. 22, line 12);

b) providing a second ligation product, whereby the second ligation product consists of a first oligonucleotide moiety comprising a recognition site for a third type IIS restriction enzyme, a second oligonucleotide moiety comprising a recognition site for a fourth type IIS restriction enzyme and a third oligonucleotide moiety, whereby the third oligonucleotide moiety is a part of the nucleic acid molecule to be manufactured, and

whereby the third and the fourth type IIS restriction enzyme each generate an overhang (hairpin oligonucleotides, anchor and splinker oligos, are provided, each with a single-stranded overhang and a restriction site for a type IIS restriction endonuclease that generates an overhang, p. 4, lines 12-16, Figure 1, top and Figures 9 and 10; oligonucleotides are ligated to form a ligation product, p. 4, lines 23-25 and Figure 1, second panel; after cleavage, another hairpin oligonucleotide is combined with the cleavage product to form a longer new product, p. 16, lines 8-10, p. 17, lines 25-29 and Figure 1, fourth panel), whereby the overhang generated by the third type IIS restriction enzyme has a length which is different from the length of the overhang generated by the fourth type IIS restriction enzyme (sets of anchor and splinker oligonucleotides can contain combinations of different restriction enzyme recognition sequences, including those with one-, two- or four-base overhangs, p. 21, line 28 to p. 22, line 12);

c) cutting the first ligation product with the second restriction enzyme generating a first cut ligation product and cutting the second ligation product with the fourth restriction enzyme generating a second cut ligation product (ligation products are cleaved by treatment with a type II restriction enzyme such as Eco31I, Esp3I and Bpi I, which cleave outside their recognition sequence to release an elongated product containing an overhang, with part of the anchor sequence remaining with the splinker sequence, p. 4, lines 28-31, p. 15, line 28 to p. 16, line 8, , p. 17, lines 22-25, Figure 1, third panel and Figure 12);

d) providing a third at least partially double-stranded oligonucleotide and ligating the third oligonucleotide with the first cut ligation product, whereby the third

oligonucleotide comprises an overhang which is complementary to the overhang of the first cut ligation product generated in step c) and whereby the third oligonucleotide comprises a recognition site for a fifth IIS restriction enzyme (after cleavage of the new ligation products, another hairpin oligonucleotide containing a type IIS restriction enzyme site is combined with the cleavage product to form a longer new product, p. 16, lines 8-10, p. 17, lines 25-29 and Figure 1, fourth panel);

e) providing a fourth at least partially double-stranded oligonucleotide and ligating the fourth oligonucleotide to the second cut ligation product, whereby the fourth oligonucleotide comprises an overhang which is complementary to the overhang of the second ligation product generated in step c) and whereby the fourth oligonudeotide comprises a recognition site for a sixth type IIS restriction enzyme (after cleavage of the new ligation products, another hairpin oligonucleotide containing a type IIS restriction enzyme site is combined with the cleavage product to form a longer new product, p. 16, lines 8-10, p. 17, lines 25-29 and Figure 1, fourth panel; a variety of different type IIS restriction enzymes are available, p. 21, line 28 to p. 22, line 12);

f) immobilizing the ligation product of step d) and step e) on a surface by means of a modification of the third oligonucleotide and the fourth oligonucleotide (the lengthened ligation product is immobilized via the anchor oligo through a biotin moiety to a solid matrix such as a bead containing streptavidin, p. 13, lines 13-19 and 24-29);

g) and h) cutting the immobilized ligation products of step d) with the fifth and third type IIS restriction enzyme releasing an oligonucleotide (ligation products are cleaved by treatment with a type II restriction enzyme such as Eco31I, Esp3I and Bpi I,

which cleave outside their recognition sequence to release an elongated product containing an overhang, with part of the anchor sequence remaining with the splinker sequence, p. 4, lines 28-31, p. 15, line 28 to p. 16, line 8, , p. 17, lines 22-25, Figure 1, third panel and Figure 12); and

i) combining and ligating the oligonucleotide released according to step g) with the immobilized reaction product of step h), whereby the overhang generated by the first and the third restriction enzyme is complementary to the overhang generated by the fifth and sixth restriction enzyme (hairpin oligonucleotides are ligated after hybridization of their complementary overhangs, p. 4, lines 23-25, p. 16, lines 8-10 and Figure 1, second panel).

With regard to claim 34, Schatz teaches a method wherein the first and the third restriction enzyme are identical and/or the second and the fourth restriction enzyme are identical and/or the fifth and the sixth restriction enzyme are identical (the ligation product can then be cleaved with a restriction endonuclease specific to the anchor oligo to yield a lengthened splinker product, which can be cleaved by the same enzyme originally used to generate the first ligation product, p. 18, lines 1-3 and Figure 1, panels 4 and 5).

With regard to claim 35, Schatz teaches a method wherein the first and the third restriction enzyme and the fifth and the sixth restriction enzyme are each a restriction enzyme generating a four nucleotide overhang, preferably at the 5' end (5'-overhangs of four nucleotides are produced with restriction enzymes Esp3I, Bpi I or BsaI, p. 15, line 28 to p. 16, line 10 and Figures 9, 10 and 12).

With regard to claim 36, Schatz teaches a method wherein the second and the third restriction enzyme is a restriction enzyme creating an overhang having a length which is selected from the group comprising 1, 2, 3, 4, 5 and 6 nucleotides (sets of anchor and splinker oligonucleotides can contain combinations of different restriction enzyme recognition sequences, including those with one-, two- or four-base overhangs, p. 21, line 28 to p. 22, line 12).

With regard to claim 37, Schatz teaches a method wherein the first and the second restriction enzyme is Esp3I or Eco31I and the fifth and the sixth restriction enzyme is Eco31I or Esp3I (ligation products are cleaved by treatment with a type II restriction enzyme such as Eco31I and Esp3I, which cleave outside their recognition sequence to release an elongated product containing an overhang, with part of the anchor sequence remaining with the splinker sequence, p. 4, lines 28-31, p. 15, line 28 to p. 16, line 8, , p. 17, lines 22-25, Figure 1, third panel and Figures 9 and 12).

With regard to claim 38, Schatz teaches a method wherein the ligation product of step i) is used as a first ligation product and/or a second ligation product and steps a) to i) are repeated one or several times (cycle of ligation, cleaving, and washing allows another cycle to start and produce increasingly longer products wherein ligation products are ligated to new hairpin oligonucleotides containing a type IIS restriction enzyme site and a modification such as biotin, p. 16, lines 14-17, Figure 1, bottom panel and Figure 14).

With regard to claim 39, Schatz teaches a method wherein the third moiety is arranged between the moieties of the oligonucleotides containing the restriction site for

the type IIS restriction enzymes (nucleotides indicated as N bases within the overhang of the splinker oligonucleotide, are located between restriction sites used to cleave the next ligation product that results in an extended product, p. 16, lines 8-10, p. 17, lines 25-29 and Figure 1, panel 4).

With regard to claim 40, Schatz teaches a method wherein the first and the second ligation products are provided in separate reaction vessels (the lengthened ligation product is transferred to a new reaction container and bound to a new anchor oligo via the overlapping regions for further ligation, p. 16, lines 8-10, p. 17, lines 25-29 and Figure 1, fourth panel).

With regard to claim 42, Schatz teaches a method wherein the ligation product of step f) is combined and ligated with an elongated oligonucleotide according to any of the preceding claims, whereby this ligation product is used as a first or a second ligation product in step a) or step b) in the method of claim 41 (ligation products comprising hairpin oligonucleotide are cleaved and ligated to an elongated oligonucleotide that undergoes successive ligations starting with the original splinker oligonucleotide to produce long double-stranded products within several hours (p. 18, lines 22-31 and Figure 14).

With regard to claim 43, Schatz teaches a method wherein the DNA fragment is the nucleic acid molecule or part thereof which is to be manufactured (elongated oligonucleotides that are ligated to a newly-cleaved ligation product represent the oligonucleotide that is being produced, extended each cycle when a ligation product is

ligated and then cleaved again, p. 16, lines 8-10, p. 17, lines 25-29, Figure 1, fourth panel and Figure 14).

With regard to claim 44, Schatz teaches a method wherein the third moiety is arranged between the moieties of the oligonucleotides containing the restriction site for the type IIS restriction enzymes (nucleotides indicated as N bases within the overhang of the splinker oligonucleotide, are located between restriction sites used to cleave the next ligation product that results in an extended product, p. 16, lines 8-10, p. 17, lines 25-29 and Figure 1, panel 4).

Conclusion

7. Claims 23-44 are rejected. No claims are allowable.

Correspondence

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

/David C Thomas/
Examiner, Art Unit 1637